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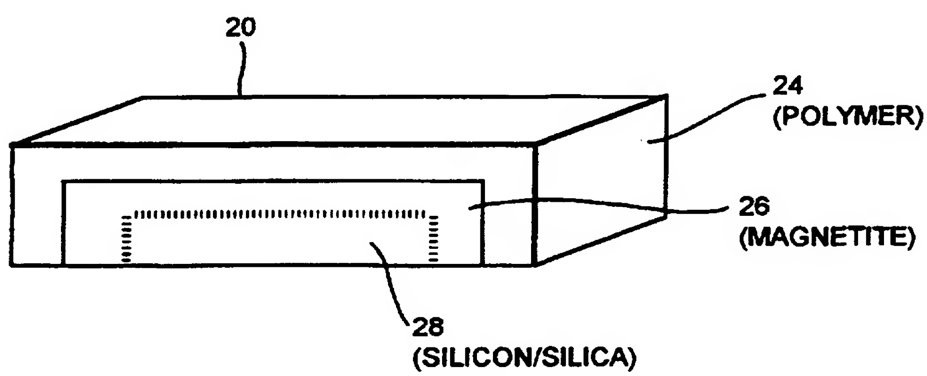


(57) Abstract

The present invention relates to a composite. The composite comprises (i) a support (20); (ii) at least a first material bound to the support (20); and (iii) at least a first readable marking (30) present on and/or in the support (20) wherein the first readable marking (30) is capable of indicating the presence of the first material.

A COMPOSITE FOR COMBINATORIAL ORGANIC SYNTHESIS

The present invention relates to a composite. In addition, the present invention relates to a process of forming the composite. The present invention also relates to the use of that composite to prepare products.

In particular the composite of the present invention is useful in combinatorial chemistry, especially combinatorial organic synthesis of products.

Combinatorial chemistry is a valuable tool for synthetic chemistry. It allows extremely large numbers of products to be synthesised in a reasonable time frame. In short, the products are synthesised by a multi-step wise addition of materials (such as molecules) to another material (such as a molecule) or other materials (such as molecules) that have been already linked together. The synthesised products can then be screened to see if, for example, they show promising favourable biological activity.

Introductory reviews on combinatorial chemistry can be found in the teachings of Gallop *et al* (*J Med Chem* **1994**, 37, 1233) and Gordon *et al* (*J Med Chem* **1994**, 37, 1385).

The application of combinatorial chemistry has led to the preparation of libraries of different benzodiazepines (WO95/02566), phenolic derivatives (Leznoff *Acc Chem Res* 1978, 11, 327-333), endothelin antagonists (Bunin *et al* PNAS 1994, 91, 4708-4712) and α1-adrenergic antagonists (Furka *et al*, *Int J Peptide Protein Res*, 1991, 37, 487-493).

One problem with combinatorial chemistry is the isolation of products from the synthetic reaction medium or media. To solve this problem, Szymonifka and Chapman (Tetrahedron Letters, 1995, vol 36, No. 10, pp1597-1600) proposed the use of magnetically manipulable polymeric supports for solid phase organic combinatorial synthesis of products.

According to Szymonifka and Chapman (*ibid*):

> "*Typically, in combinatorial organic synthesis, an appropriately functionalized solid phase support is partitioned among a number of reactors and unique subunits are reacted with each pool of resin in each reactor. The resin beads are then removed entirely from all reactors, combined and mixed until homogeneous. This mixture is then redistributed to the reactors and the process is repeated, usually with a different set of unique subunits. If there are no redundancies in the subunits, the number of compounds produced by such a scheme is the number of reactors expanded to the exponent of the number of steps in which subunits are coupled. Thus, three sequential reactions using twenty pools of resin and unique subunits affords 20^3 products.*"

In more detail, however, reference shall now be made to Figure 1 which presents a schematic diagram of the use of polymeric supports for solid phase organic combinatorial synthesis of products. These supports, which for example are magnetite-impregnated poly(vinylbenzene), are sometimes referred to as "beads". In addition, the synthetic steps using such beads are sometimes referred to as "split bead synthesis" or "split/mix synthesis".

In the combinatorial synthetic process shown in Figure 1, an ensemble of, for example 900, beads (wherein each bead will be referred to as 1', but is not shown as such) is collectively shown as set (1) of beads. The set (1) of beads is divided into three portions (3, 5, 7) of beads - each having for example 300 beads. This explains why set (1) of beads is schematically shown bigger than portions (3, 5, 7) of beads. Thus, each of the portions (3, 5 and 7) of beads will initially contain equal amounts of beads (1').

Material A - such as reactant molecule A - is then bound (also referred to as coupled) to each bead (1') of the portion (3) of beads, such as via a suitable linker group (not shown), by use of a suitable reaction medium or media (not shown).

Typically, an excess of material A will be added to the portion (3) of beads to ensure the binding of at least one material A to each bead (1') of the portion (3) of beads. Each bead in the portion (3) of beads having bound thereto the material A will be referred to as bead (3', but is not shown as such).

A similar operation is also performed for the beads (1') in portion (5) of beads with material B. Each bead in the portion (5) of beads having bound thereto the material B will be referred to as bead (5', but is not shown as such).

A similar operation is also performed for the beads (1') in the portion (7) of beads with material C. Each bead in the portion (7) of beads having bound thereto the material C will be referred to as bead (7', but is not shown as such).

When the beads (3', 5' and 7') in the portions (3, 5 and 7, respectively) of beads have been formed, each of the portions (3, 5 and 7) of beads is then extracted from each reaction medium by use of, for example, a magnet (not shown). The beads (3', 5' and 7') are then recombined to form a mixture of different beads (not shown) - comprising for example 900 beads.

The beads (3'), the beads (5') and the beads (7') within the mixture of different beads are then thoroughly mixed to form a set (10) of beads in a homogeneous mixture.

The set (10) of beads is then divided into three portions (13, 15, 17) of beads - of for example 300 beads each. This explains why set (10) of beads is schematically shown bigger than the portions (13, 15, 17) of beads. On average, therefore, in each portion (13, 15 and 17) of beads there will be an equal number of beads (3', 5' and 7').

Material A - such as reactant molecule A - is then linked (also referred to as coupled) to the material bound to each of the beads (3'), beads (5') and beads (7') in the portion (13) of beads, such as by a linking reaction of the materials in a suitable reaction medium or media (not shown).

Typically an excess of material A will be added to the portion (13) of beads to ensure the linking of material A to the material bound to each bead in the portion (13) of beads. This linking step (also known as coupling step) will produce the products AA, BA and CA bound to individual beads. Each of these particular beads in portion (13) of beads will be collectively referred to as bead (13', but is not shown as such). [The second A can be different from the first A. Also, A can be the same as or different from B which can be the same as or different from C.]

A similar operation is performed for the beads (5') in the portion (15) of beads with material B. This linking step (also known as a coupling step) produces the products AB, BB and CB bound to individual beads in the portion (15) of beads. Each of these particular beads in the portion (13) of beads will be collectively referred to as bead (13', but is not shown as such). [The second B can be different from the first B. Also, A can be the same as or different from B which can be the same as or different from C.]

A similar operation is also performed for the beads (7') in the portion (17) of beads with material C. This linking step (also known as a coupling step) produces the products AC, BC and CC bound to individual beads in portion (17). Each of these particular beads in the portion (17) of beads will be collectively referred to as bead (17', but is not shown as such). [The second C can be different from the first C. Also, A can be the same as or different from B which can be the same as or different from C.]

When the beads (13', 15' and 17') have been formed in the portions (13, 15 and 17, respectively) of beads, they are then extracted from each reaction medium by use of as a magnet (not shown). The beads (13'), the beads (15') and the beads (17') and are then recombined to form a set (18) of different beads - of which there may be for example 900 beads.

The steps of dividing, linking (also referred to as coupling) and recombining are then continued until a desired number of different products are formed.

The products can then be separated from the bead by application of a suitable cleavage step. The products can then be screened for favourable biological activity using, for example, *in vitro* assays.

If a product shows a favourable property it can then be analysed - such as by standard analytical techniques - such as NMR and/or MS techniques.

However, despite the ability to form a large number of products by the conventional split bead synthesis, these products can not be readily analysed by such techniques, since the exact identity of the materials on the beads has been lost during the synthetic process steps.

Attempts to overcome this problem include the analytical scheme proposed by Salmon *et al* (PNAS, 1993, 90, 11708-11712). In this scheme, when the split bead synthesis has finished the beads are split up into groups of, for example, from 30 to 500, and a portion of the synthesised product is cleaved off into solution. The groups of beads corresponding to the most active pools are then split to single beads, and a second portion of the compound released and assayed. The beads associated with the most active compounds can then be submitted for structure determination. However, the success of this method depends on the linker between the bead and the product. A further problem with this scheme is that one has to determine the structure of the active product from the amount remaining on a single bead; and this is often only in minuscule amounts.

A further attempt to overcome the inherent problem of analysing the synthesised product include the use of tags associated with materials bound to the beads, which tags are individual to each type of material. Accordingly, the product of interest may be indirectly analysed by determining the presence of a number of individual tags. Examples of the use of tags have been proposed by Needels *et al* (PNAS, 1993, 90, 10700-10704) and J C Chabala (*Perspectives in Drug Discovery and Design*, 1994, 2, 305-318).

Examples of such tags include "soft" tags such as oligopeptides and oligonucleotides.

Other examples of tags include "hard" tags such as electrophoretic tags - such as the group -O-$(CH_2)_n$-O-AR.

One disadvantage of these types of tagging is that it requires extra synthetic steps to introduce the tags and the tag chemistry may not be compatible with the synthesis of different classes of products.

Another example of a tag is radio-frequency tag encoding. However, radio-frequency tagging has a problem in that it has a population limitation.

The present invention seeks to overcome the problems associated with the prior art analytical techniques for the analysis of materials, and products that have been formed therefrom.

According to a first aspect of the present invention there is provided a composite comprising (i) a support; (ii) at least a first material bound to the support; and (iii) at least a first readable marking present on and/or in the support, wherein the first readable marking is capable of indicating the presence of the first material.

According to a second aspect of the present invention there is provided the use of a composite according to the present invention for the synthesis of a product, wherein the product is synthesised by reacting the first material of the composite with a second material.

According to a third aspect of the present invention there is provided a process of synthesising a product comprising reacting at least a first material with a second material, characterised in that the first material is bound to a support, wherein a first readable marking is present on and/or in the support which first readable marking is capable of indicating the presence of the first material; and wherein a second readable marking is present on and/or in the support which second readable marking is capable

of indicating the presence of a second material.

According to a fourth aspect of the present invention there is provided a process of synthesising a product comprising reacting at least a first material with a second material, characterised in that the reaction comprises the following steps: forming a composite according to the present invention; introducing a readable marking in and/or on the support of the composite, which readable marking is capable of indicating the presence of the second material; and linking the first material with the second material.

According to a fifth aspect of the present invention there is provided a product obtained by a use according to the present invention or by a process according to the present invention.

According to a sixth aspect of the present invention there is provided a product according to the present invention wherein the product is or is used in the production of a pharmaceutical.

According to a seventh aspect of the present invention there is provided a composite comprising: (i) a support; (ii) a product bound to the support, wherein the product has been synthesised by reacting at least a first material bound to the support with at least a second material; and (iii) a readable marking or a series of readable markings present in and/or on the support, wherein the readable marking or the series of readable markings is capable of indicating the synthetic history of the product.

According to an eighth aspect of the present invention there is provided the use of a composite according to the present invention in combinatorial chemistry.

One of the key advantages of the present invention is that it provides a means for determining more readily the synthetic history of a product of interest, rather than having to analyse the product itself.

A further key advantage is that libraries of products can be prepared on solid supports using automated robotic set-ups and wherein the synthetic history of those products can be readily determined - such as by a machine.

The composite of the present invention provides an alternative analytical tool to current soft or hard chemical tag strategies. Moreover, the composite of the present invention amplifies synthetic procedures that can be used in split bead synthesis simply because tagging and library synthesis must use reagents of orthogonal reactivity.

The term "capable of indicating the presence of" as used herein includes a readable marking that is indicative of the presence of a bound material and/or the number of the reaction step(s), which readable marking may be an optically readable code. The term also includes the marking being a sensor on or of the support whose detectable characteristics change when different materials and/or number of materials are bound to the support. Preferably, the term means an optically readable marking - such as a code - that is indicative of at least the presence of a bound material. More preferably, the term a readable marking that is indicative of the presence of a bound material and the number of synthetic steps. More preferably, the marking is machine readable - thus synthesis, screening and analysis can be fully automated.

The composite may be separated from a reaction medium by, for example, filtration techniques. Preferably, however, the composite comprises a separating component, such as a magnetic separating component (e.g. magnetite). The use of a magnetic separating component is advantageous as it eases separation of the composite from a reaction medium by use of a magnet. In addition, the use of a magnetic separating component is further advantageous in that it allows the composite to be held in a particular orientation to enable a marking to be read from and written onto the support with more ease.

With the present invention, there may be occasions when the products are to be assayed when bound to the support.

For example, it may be desirable to have a biologically active entity bound to a support - so that the entity can be put into a reaction medium for a period of time and then easily retracted from it.

In the alternative, however, preferably there is a cleavable linker between the first material and the support. The presence of such a linker would allow the synthesised product to be isolated from the reaction medium and separated from the support more easily.

Preferably at least a second material is linked to the first material; and wherein at least a second readable marking is present on and/or in the support, wherein the second readable marking is capable of indicating the presence of the second material.

Thus, a third material may be linked to the second material; and wherein at least a third readable marking is present on and/or in the support, wherein the third readable marking is capable of indicating the presence of the third material.

Expressed in an alternative fashion, an n^{th} material may be linked to an $n\text{-}1^{th}$ material; and wherein at least an n^{th} readable marking and an $n\text{-}1^{th}$ readable marking are present on and/or in the support, wherein the n^{th} readable marking is capable of indicating the presence of the n^{th} material, wherein the $n\text{-}1^{th}$ readable marking is capable of indicating the presence of the $n\text{-}1^{th}$ material; and wherein n is an integer greater than 1.

Preferably, one or more further readable markings are present on and/or in the support, wherein the or each further readable marking is capable of indicating the presence of each step of forming the composite.

Preferably, each readable marking is an optically readable marking. Preferably, each readable marking is a visually readable code.

Preferably, each readable marking is formed in and/or on the support.

Preferably, the support comprises a semi-conductor component on and/or in which component is any one or more readable marking.

Preferably, the support comprises silicon and/or silica.

Preferably, the composite comprises (iv) a component that enables the composite to be separated from a reaction medium.

Preferably, the component is magnetic.

Preferably, the component is magnetite.

Preferably, the composite comprises (v) a polymeric surface to which the first material is bound.

Preferably, the polymeric surface does not cover each readable marking.

Preferably, the polymeric surface is polystyrene.

Preferably, the first material is bound to the support *via* a cleavable linker group.

Preferably, a plurality of first materials are bound to the support.

Preferably, the composite is of a particulate structure.

Preferably, the support is a bead.

Preferably, wherein each material is a molecule.

Preferably, step ii precedes step iii.

Typically, the size of the support is in the order of 1mm x 1mm x 1 mm or less.

Preferably, the size of the support is less than 1mm x 1mm x 1 mm. For example, a preferred suitable support for the present invention is a microparticle that has a thickness of from 0.1μm to 50μm, a length of from 0.1μm to 50μm, and a width of from 0.1μm to 50μm. Preferably the support of the present invention is a microparticle that has a thickness of about 10 μm, a length of about 10μm, and a width of about 10μm.

Another example of a suitable support for the present invention can be found in GB-A-2289150. This support comprises a microparticle wafer that has a thickness of from 0.1μm to 5μm and a length of from 0.5μm to 50μm.

In the present invention, the readable marking is distinct from the material that is bound to the support.

The resultant product can be synthesised from a plurality of materials, all of which may be the same, some of which may be the same or all of which are different.

Each support can have bound thereto a plurality of products.

The synthetic process of the present invention is applicable to any chemical reaction, especially organic chemical transformation. In particular, the present invention is applicable to any one or more of the following reactions: photochemical release (e.g. use of any one or more of ortho-nitro-benzyl linkers, HF/TFA scission of silane linkers, metal metathesis of alkene linkers with ethylene); organometallic methods to construct carbon-carbon skeletons (e.g. using any one or more of palladium and nickel [0] chemistry, alkene metathesis, asymmetric hydrogenation and hydroformylation); iterative aldol reactions; cycloaddition reactions; heterocyclisations; redox chemistry; transacylations; and alkylations.

In a highly preferred embodiment, the support is a polymer-magnetite-silicon or magnetite-silicon-silica-silicone polymer composite, and wherein the readable marking is a bar code etched onto the support.

The magnetite core can be used in solution phase/solid phase separations and, at the same time, be used to align single beads for micro code writing/reading in the silicon face.

In a preferred embodiment, the combinatorial synthesis will be effected *via* phase methods using, for example, polystyrene supports with cleavable linkers. Examples of such linkers are those that are cleavable either *via* photochemically or *via* gas/solid phase reactions. Possible cleavage techniques include laser-mediated thermal cycloelimination-recycloaddition with alkynes (eg in an ethyne atmosphere) followed by spontaneous loss of polymer-OL *via* aromatisation or *via* gas-solid phase protodesilylation reactions.

In addition, the preferred magnetite-silicon-silica-silicone composites may be employed with alkylsilane triol linkers attached to the silica modified silicon surface. Such linkers could be subject to either photochemical or gas-solid phase cleavage.

If the order of the materials to be added is always known then it may not be necessary to include readable markings that are indicative of the number of the reaction step. However, preferably such readable markings are present in and/or on the support.

If the same series of reactions are to carried out with the same composite materials and the order of the materials to be added is always known then it may not be necessary to include readable markings indicative of the materials as such. In this instance, the readable markings for the number of each reaction step would be sufficient to be indicative of the presence of the materials bound to the support. However, preferably such readable markings are present in and/or on the support.

In summation therefore the present invention provides a composite comprising (i) a support; (ii) at least a first material bound to the support; and (iii) at least a first readable marking present on and/or in the support, wherein the first readable marking is capable of indicating the presence of the first material.

The present invention also provides a composite comprising: (i) a support; (ii) a product bound to the support, wherein the product has been synthesised by reacting at least a first material bound to the support with at least a second material; and (iii) a readable marking or a series of readable markings present in and/or on the support, wherein the readable marking or the series of readable markings is capable of indicating the synthetic history of the product.

Thus the present invention allows extremely large numbers of compounds to be synthesised and categorised in a reasonable time frame. It is believed that using the present invention it will be possible to fabricate, evaluate and archive up to 10,000, or even up to 1,000,000, compounds within 24 hours.

The present invention will now be described only way of example in which reference shall be made to the following figures, in which:

Figure 1 is a schematic diagram of a conventional split bead synthesis method;

Figure 2 is an enlarged perspective view of a preferred support according to the present invention;

Figure 3 is an enlarged view of a preferred support according to the present invention showing the presence of a series of markings according to the present invention; and

Figure 4 is a schematic diagram of a split bead synthesis process according to the present invention.

Figure 1 has been discussed above.

With reference to Figures 2 and 3, the support (20) comprises a polymeric outer layer (24) to which can be attached a suitable material (not shown), such as a reactant molecule via a suitable linker group (not shown).

The support (20) also comprises a layer of magnetite (26), which aids the recovery of the composite material of the present invention from a reaction medium.

The support (20) also comprises a silicon/silica core (28), on to which can be etched a marking (or markings) (30) that is (are) indicative of the material(s) directly bound to the support and the material(s) that are linked to the material(s) bound to the support.

The series of markings (30) shown in Figure 3 are as follows:

· (32)	denotes the first reaction, namely binding of the first material (not shown) to the support (20) by a suitable linker group (not shown)
| ▌ (34)	denotes the first material which marking, here a code, will be unique for the first material - such as reactant material C as shown in Figure 4
: (36)	denotes the second reaction namely linking of the second material (not shown) to the first material (not shown) bound to the support (20) by a suitable linker group (not shown)
| (38)	denotes the second material which marking, here a code, will be unique for the second material - such as reactant material A as shown in Figure 4

Figure 4 shows a highly preferred use of the composite of the present invention. In this regard, Figure 4 is a schematic diagram of a combinatorial synthetic process according to the present invention.

In the combinatorial synthetic process shown in Figure 4, an ensemble of, for example 900, beads (wherein each bead will be referred to as 101', but is not shown as such) is collectively shown as set (101) of beads. The set (101) of beads is divided into three portions (103, 105, 107) of beads - each having for example 300 beads. This explains why set (101) of beads is schematically shown bigger than portions (103, 105, 107) of beads. Thus, each of the portions (103, 105 and 107) of beads will initially contain equal amounts of beads (101').

Preferably, the beads (101') comprise the support (20) shown in Figures 2 and 3.

Each bead (101') in the portion (103) of beads is marked with a unique readable marking that is indicative of the number of the reaction step that is to be carried out (here the marking is ·) and with a unique readable marking that is indicative of the material that is to be bound to the support (here the marking is (|). In Figure 4, that material is shown as reactant A.

Each bead (101') in the portion (105) of beads is also marked with a unique readable marking that is indicative of the number of the reaction step that is to be carried out (here the marking is ·) and with a unique readable marking that is indicative of the material that is to be bound to the support (here the marking is (▌). In Figure 4, that material is shown as reactant B.

Each bead (101') in the portion (107) of beads is also marked with a unique readable marking that is indicative of the number of the reaction step that is to be carried out (here the marking is ·) and with a unique readable marking that is indicative of the material that is to be bound to the support (here the marking is (| ▌). In Figure 4, that material is shown as reactant C.

The layer of magnetite (26) in each of beads (101') assists in the marking of the beads (101'). In this regard, use of a magnet (not shown) will hold the areas of the silicon/silica core (28) in a certain orientation for the subsequent marking thereof and for the reading of the marking.

Reactant A is then bound (also referred to as coupled) to each bead (101') of the portion (103) of beads, such as via a suitable linker group (not shown), by use of a suitable reaction medium or media (not shown). Typically, an excess of material A will be added to the portion (103) of beads to ensure the binding of at least one material A to each bead in the portion (103) of beads. Each bead in the portion (103) of beads having bound thereto the material A will be referred to as bead (103', but is not shown as such).

A similar operation is also performed for the beads (101') in the portion (105) of beads with material B. Each bead in the portion (105) of beads having bound thereto the material B will be referred to as bead (105', but is not shown as such).

A similar operation is also performed for the beads (101') in the portion (107) of beads with material C. Each bead in the portion (107) of beads having bound thereto the material C will be referred to as bead (107', but is not shown as such).

When the beads (103', 105' and 107') in the portions (103, 105 and 107, respectively) of beads have been formed, they are then extracted from each reaction medium by use of, for example, a magnet (not shown). The beads (103', 105' and 107') are then recombined to form a mixture of different beads (not shown) - which mixture may for example comprise 900 beads.

The beads (103'), the beads (105') and the beads (107') within the mixture of different beads are then thoroughly mixed to form a set (110) of beads in a homogeneous mixture.

The set (110) of beads is then divided into three portions (113, 115, 117) of beads - of for example 300 beads each. This explains why set (110) of beads is schematically shown bigger than portions (113, 115, 117) of beads. On average, in each portion (113, 115 and 117) of beads there should be an equal number of beads (103', 105' and 107').

Each bead in the portion (113) of beads is then marked with a unique readable marking that is indicative of the number of the reaction step that is to be carried out (here the marking is :) and with a unique readable marking that is indicative of the material that is to be linked to the bound material (here the marking is (|). In Figure 4, that material is shown as reactant A.

Each bead in the portion (115) of beads is also marked with a unique readable marking that is indicative of the number of the reaction step that is to be carried out (here the marking is :) and with a unique readable marking that is indicative of the material that is to be linked to the bound material (here the marking is (▮). In Figure 4, that material is shown as reactant B.

Each bead in the portion (117) of beads is also marked with a unique readable marking that is indicative of the number of the reaction step that is to be carried out (here the marking is :) and with a unique readable marking that is indicative of the material that is to be linked to the bound material (here the marking is (| ▮). In Figure 4, that material is shown as reactant C.

Material A - such as reactant molecule A - is then linked (also referred to as coupled) to the material bound to each of the marked beads in the portion (113) of beads, such as by a linking reaction of the materials in a suitable reaction medium or media (not shown). Typically an excess of material A will be added to the portion (113) of beads to ensure the linking of material A to the material bound to each bead in the portion (113) of beads. This linking step (also known as coupling step) produces the products AA, BA and CA bound to individual beads. Each of these particular beads in portion (113) of beads will collectively be referred to as bead (113', but is not

shown as such).

A similar operation is performed for the beads in portion (115) of beads with material B. This linking step (also known as a coupling step) produces the products AB, BB and CB bound to individual beads in the portion (115) of beads. Each of these particular beads in portion (115) will collectively be referred to as bead (115', but is not shown as such).

A similar operation is also performed for the beads in the portion (117) of beads with material C. This linking step (also known as a coupling step) produces the products AC, BC and CC bound to individual beads in the portion (117) of beads. Each of these particular beads in portion (117) will collectively be referred to as bead (117', but is not shown as such).

When the beads (113', 115' and 117') have been formed in the portions (113, 115 and 117, respectively) of beads, they are then extracted from each reaction medium by use of as a magnet (not shown). The beads (113'), the beads (115') and the beads (117') and are then recombined to form a mixture (118) of a number of different beads - in which there may be for example 900 beads.

The steps of dividing, linking (also referred to as coupling) and recombining are then continued until a desired number of different products are formed.

Thus, the synthetic process of the present invention produces products bound to supports, wherein the products have been formed by step wise synthetic stages which comprise successive linking of materials, which materials may be the same, partially the same or different, and wherein the supports have readable markings thereon and/or therein which are indicative of the synthetic history of the products.

The products obtained and whilst still bound to the beads can then be screened for favourable biological activity using, for example, *in vitro* assays. This is sometimes referred to as "single bead assay".

Alternatively, the products can then be separated from the bead by application of a suitable cleavage step.

The products can then be screened for favourable biological activity using, for example, *in vitro* assays.

Even though the markings shown in these examples are dots and lines, including combinations thereof, other suitable readable markings can be used.

Even though the reactant materials in the above-mentioned first and second synthetic steps as being A, B and C, it is to be noted that reactant A in the second synthetic step could be the same as reactant A in the first synthetic step. Likewise, reactant A in the second synthetic step could different to reactant A in the first synthetic step. Likewise, it is to be noted that reactant A in any of the synthetic steps could be the same as any one of the reactants B and C. The same is true of the other reactants.

In addition, the beads can be split into any number of portions, which may be the same or different.

In addition, each bead can have bound to it a plurality of first materials.

<u>Preparation of Peptide Libraries</u>

Following the above procedure a tripeptide library is produced. In this, the support is a polymer matrix comprising a markable surface. An example of such a polymer matrix is modified polystyrene (e.g. a Link resin or a Wang resin). Three portions of beads are formed during each synthesis step, however any number of portions can be formed. The first material is a protected amino acid (first amino acid). The first amino acids may be the same or different for each of the portions. For example, each first material can be an FMOC protected amino acid such as any one of Arg, His and Lys. The second material is also a protected amino acid (second amino acid). The second amino acids may be the same or different for each of the portions

and/or the same as or different from any one or more of the first amino acids. For example, the second material can be an FMOC protected amino acid such as any one of Asp, Gly and Ser. The third material, which links to the second material, is also a protected amino acid (third amino acid). The third amino acids may be the same or different for each of the portions and/or the same as or different from either any one or more of the first amino acids or any one or more of the second amino acids. For example, the third material can be an FMOC protected amino acid such as any one of Leu, Ala and Thr. The first material binds to the polymer matrix via carbodiimide mediated coupling. The second material links with the bound first material via carbodiimide mediated coupling. The third material links with the bound second material via carbodiimide mediated coupling. The readable markings are formed on the surface of the polymer matrix via photolithography. When the first material has bound to the polymer matrix the amino acid is deprotected via usage of piperidine in DMF. When the second material has linked to the bound first material the amino acid is deprotected via usage of piperidine in DMF. When the third material has linked to the bound second material the amino acid is deprotected via usage of piperidine in DMF. Thus, after three synthetic steps, 27 distinct supported tripeptides have been synthesised - each of which is identifiable by the readable markings on their supports.

The split bead synthesis of the present invention is also amenable for *in situ* assay with dye-conjugated soluble receptors or in single bead release/single cell assays. In this regard, the libraries can be screened with dye-conjugated soluble receptors, with macromolecules or even in single cell assays following release from the linker but with retention of spatial identity.

Other modifications of the present invention will be apparent to those skilled in the art.

CLAIMS

1. A composite comprising

(i) a support;

(ii) at least a first material bound to the support; and

(iii) at least a first readable marking present on and/or in the support, wherein the first readable marking is capable of indicating the presence of the first material.

2. A composite according to claim 1 wherein at least a second material is linked to the first material; and wherein at least a second readable marking is present on and/or in the support, wherein the second readable marking is capable of indicating the presence of the second material.

3. A composite according to claim 1 or claim 2 wherein one or more further readable markings are present on and/or in the support, wherein the or each further readable marking is capable of indicating the presence of each step of forming the composite.

4. A composite according to any one of the preceding claims wherein each readable marking is an optically readable marking.

5. A composite according to any one of the preceding claims wherein each readable marking is a visually readable code.

6. A composite according to any one of the preceding claims wherein each readable marking is formed in and/or on the support.

7. A composite according to claim 6 wherein the support comprises a semi-conductor component on and/or in which component is any one or more readable marking.

8. A composite according to claim 7 wherein the support comprises silicon and/or silica.

9. A composite according to any one of the preceding claims wherein the composite comprises (iv) a component that enables the composite to be separated from a reaction medium.

10. A composite according to claim 9 wherein the component is magnetic.

11. A composite according to claim 10 wherein the component is magnetite.

12. A composite according to any one of the preceding claims wherein the composite comprises (v) a polymeric surface to which the first material is bound.

13. A composite according to any one of the preceding claims wherein the polymeric surface does not cover each readable marking.

14. A composite according to claim 12 or claim 13 wherein the polymeric surface is polystyrene.

15. A composite according to any one of the preceding claims wherein the first material is bound to the support *via* a cleavable linker group.

16. A composite according to any one of the preceding claims wherein a plurality of first materials are bound to the support.

17. A composite according to any one of the preceding claims wherein the composite is of a particulate structure.

18. A composite according to any one of the preceding claims wherein the support is a bead.

19. A composite according to any one of the preceding claims wherein each material is a molecule.

20. Use of a composite according to any one of the preceding claims for the synthesis of a product, wherein the product is synthesised by reacting the first material of the composite with a second material.

21. A process of synthesising a product comprising reacting at least a first material with a second material, characterised in that the first material is bound to a support, wherein a first readable marking is present on and/or in the support which first readable marking is capable of indicating the presence of the first material; and wherein a second readable marking is present on and/or in the support which second readable marking is capable of indicating the presence of a second material.

22. A process according to claim 21 wherein the support comprises one or more further readable markings wherein the or each further readable marking is capable of indicating each reaction step.

23. A process according to claim 21 or 22 wherein the support is a support as defined in any one of claims 1 to 19.

24. A process of synthesising a product comprising reacting at least a first material with a second material, characterised in that the reaction comprises the following steps:

i. forming a composite according to claim 1;

ii. introducing a readable marking in and/or on the support of the composite, which readable marking is capable of indicating the presence of the second material; and

iii. linking the first material with the second material.

25. A process according to claim 24 wherein step ii precedes step iii.

26. A process according to claim 24 or claim 25 wherein the process comprises introducing one or more further readable markings in and/or on the support of the composite, wherein the or each further readable marking is capable of indicating each reaction step.

27. A product obtained by a use according to claim 19 or by a process according to any one of claims 21 to 26.

28. A product according to claim 27 wherein the product is or is used in the production of a pharmaceutical.

29. A composite comprising:

(i) a support;

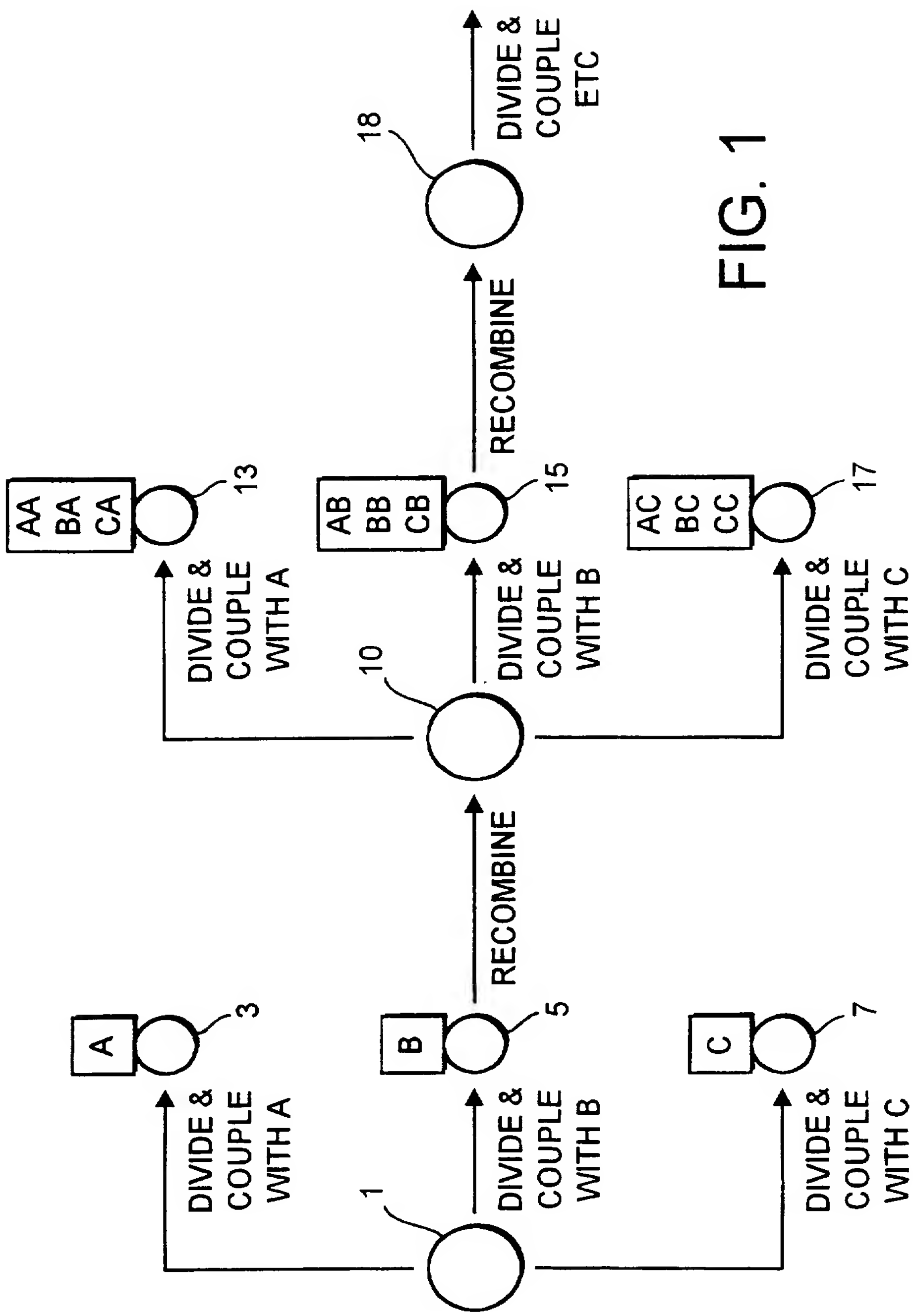
(ii) a product bound to the support, wherein the product has been synthesised by reacting at least a first material bound to the support with at least a second material; and

(iii) a readable marking or a series of readable markings present in and/or on the support, wherein the readable marking or the series of readable markings is capable of indicating the synthetic history of the product.

30. Use of a composite according to any one of claims 1 to 19, or claim 29 in combinatorial chemistry.

31. A composite substantially as hereinbefore described.

32. A process substantially as hereinbefore described.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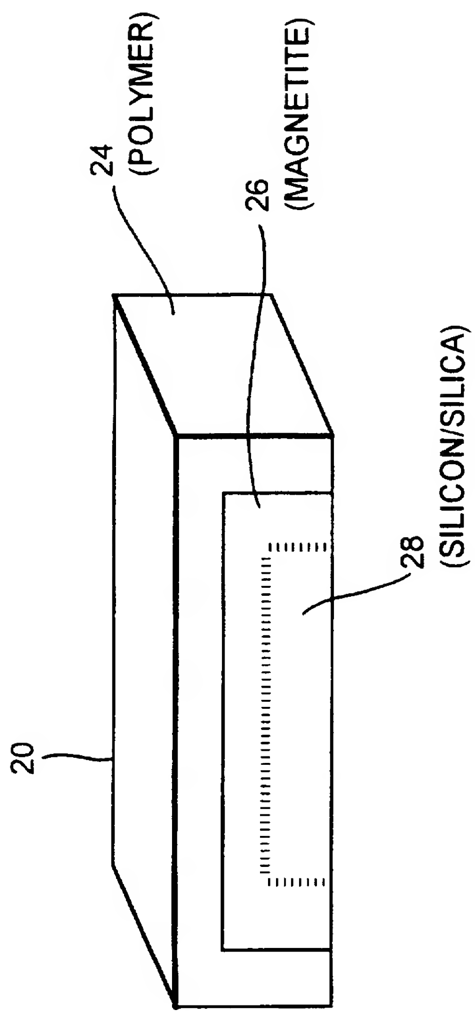
DIVIDE & COUPLE WITH B
DIVIDE & COUPLE WITH C
1
A
3
B
5
C
7
RECOMBINE
10
AA BA CA
13
AB BB CB
15
AC BC CC
17
RECOMBINE
18
DIVIDE & COUPLE ETC

FIG. 1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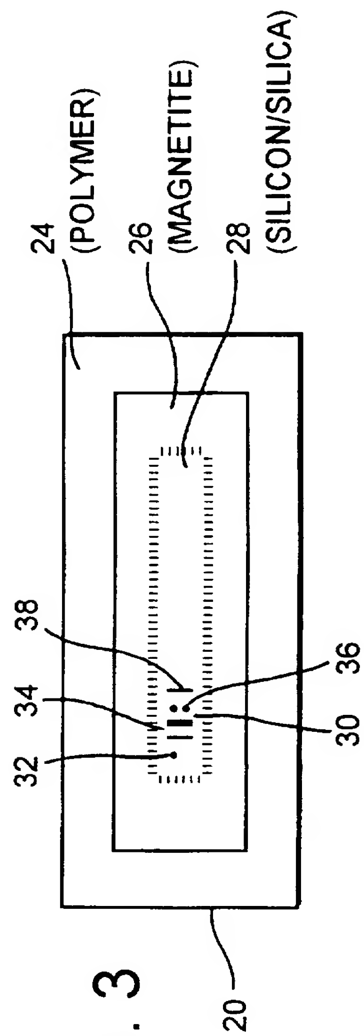
26
(MAGNETITE)
28
(SILICON/SILICA)
20

FIG. 2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(MAGNETITE)
28
(SILICON/SILICA)
38
34
32
36
30
20

FIG. 3

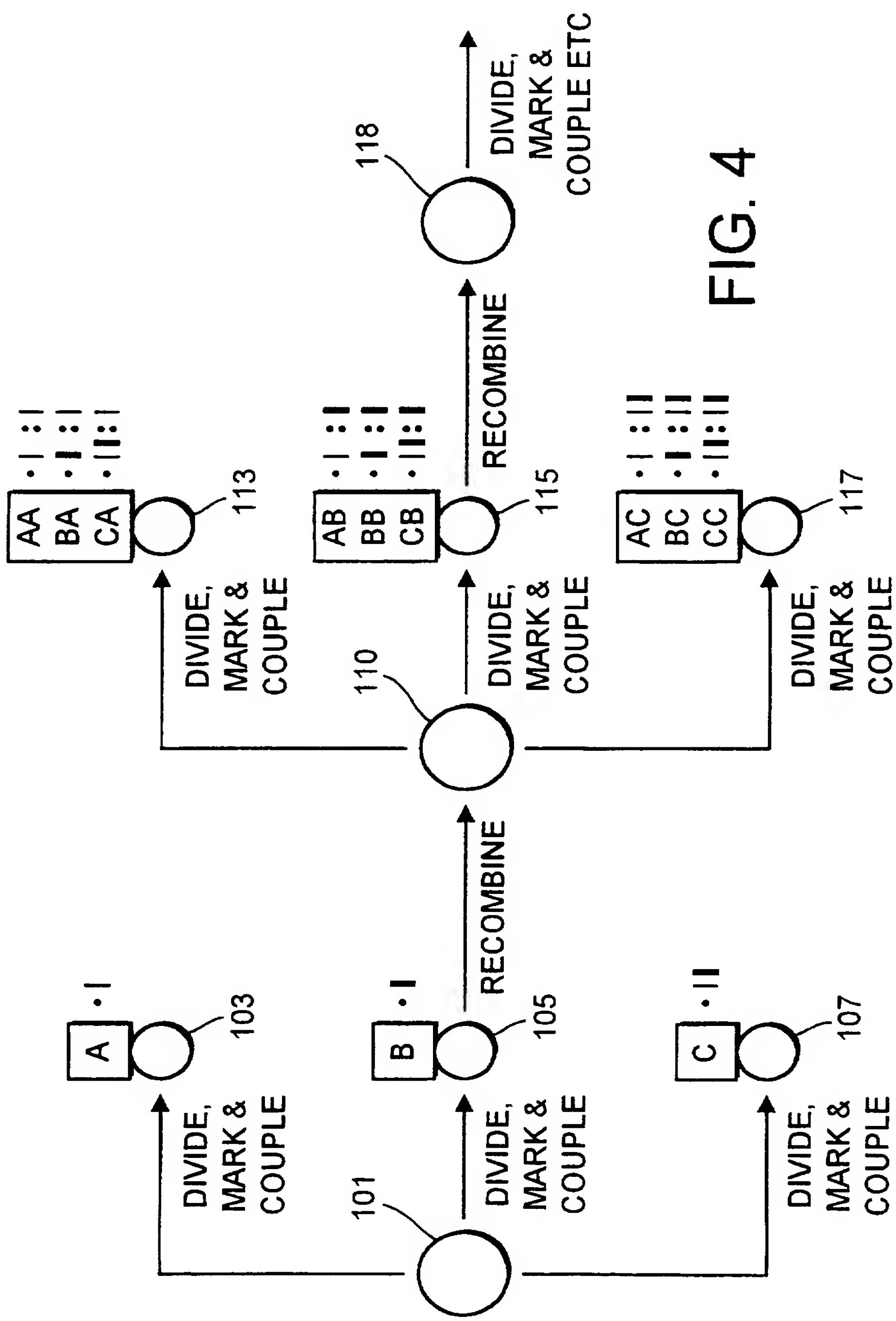
101
DIVIDE, MARK & COUPLE
DIVIDE, MARK & COUPLE
DIVIDE, MARK & COUPLE
A
103
B
105
C
107
RECOMBINE
110
DIVIDE, MARK & COUPLE
DIVIDE, MARK & COUPLE
DIVIDE, MARK & COUPLE
AA
BA
CA
113
AB
BB
CB
115
AC
BC
CC
117
RECOMBINE
118
DIVIDE, MARK & COUPLE ETC

FIG. 4

INTERNATIONAL SEARCH REPORT

International Application No
PCT/GB 97/00556

A. CLASSIFICATION OF SUBJECT MATTER
IPC 6 C07K1/04

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 6 C07K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 94 08051 A (UNIV COLUMBIA ;COLD SPRING HARBOR LAB (US); STILL W CLARK (US); OH) 14 April 1994 see claims 1,5 ---	1-6,9, 12-30
X	J.AM.CHEM.SOC., vol. 117, 1995, pages 5588-9, XP000652265 J.J.BALDWIN ET AL.: "Synthesis of a Small Molecule Combinatorial Library Encoded with Molecular Tags" see page 5588, left-hand column, line 13, paragraph 2 - line 15 --- -/--	1-3

[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

° Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

1

Date of the actual completion of the international search	Date of mailing of the international search report
12 June 1997	07.07.1997

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Deffner, C-A

Inte onal Application No
PCT/GB 97/00556

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	TRENDS BIOTECHNOL., vol. 12, no. 1, 1994, pages 19-26, XP000652268 J.W.JACOBS ET AL.: "Combinarorial Chemistry- applications of light- directed chemical synthesis" ---	
A	TERAHEDRON LETT., vol. 36, no. 10, 1995, pages 1597-1600, XP000654538 M.J.SZYMONIFKA ET AL.: "Magnetically Manipulable Polymeric Supports for Solid Phase Organic Synthesis" -----	

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INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No
PCT/GB 97/00556

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 9408051 A	14-04-94	AU 5536994 A	26-04-94
		CA 2143848 A	14-04-94
		EP 0665897 A	09-08-95
		HU 72495 A	28-05-96
		JP 8506175 T	02-07-96
		NO 951230 A	30-03-95
		US 5565324 A	15-10-96